REMARKS

Claims 1, 4, 5, 10-12, 35-37, 57-65, and 67-81 are pending in the application. Claims 2, 3, 6-9, 13-34, 38-56, and 66 have been cancelled without prejudice. Claims 1, 69, and 70 have been amended. New claims 71-81 have been added. All of the pending claims are directed to the subject matter of elected restriction group I (treatment of neuropathic pain associated with diabetic neuropathy). Support for the amendments and new claims can be found in the specification at, e.g., page 7, paragraph [0032], to page 14, paragraph [0049]. No new matter has been added.

Information Disclosure Statement

The Information Disclosure Statement filed on November 27, 2006 contained a copy of the International Preliminary Examination Report from a corresponding international patent application. All references cited in the International Preliminary Examination Report had been submitted previously to the Office in Information Disclosure Statements. It is applicant's understanding that all of those references have been considered by the Examiner, since they were all initialed on the PTO-1449 forms returned with the present Office Action.

Claim Objection

At page 3 of the Office Action, claim 2 was objected to as encompassing non-elected diseases. Claim 2 has been cancelled without prejudice, thereby obviating the objection.

35 U.S.C. §112, First Paragraph (Enablement)

At pages 4-10 of the Office Action, claims 1, 2, 4, 5, 10-12, 35-37, and 57-70 were rejected as allegedly not enabled. According to the Office Action,

> the specification, while being enabling for a method of improving the behavior tests on a mouse model of tactile allodynia and thermal hyperalgesia (Chung L5/L6 spinal nerve ligation (SNL) model) and a mouse model of diabetic neuropathy induced by streptozotocin (STZ) by administering SEQ ID NO:2 or a polypeptide consisting of aa 28-140 of SEQ ID NO:2 (NBN113) to the test mice,

does not reasonably provide enablement for a method of treating all neuropathic pains in a subject comprising administering all neublastin polypeptides to the subject as broadly claimed.

Applicant respectfully traverses the rejection in view of the claim amendments and the following remarks.

Amended independent claim 1 is directed to a method for treating neuropathic pain associated with diabetic neuropathy by administering to a subject, via systemic delivery, a therapeutically effective amount of a neublastin polypeptide that exhibits neurotrophic activity and comprises an amino acid sequence that is at least 85% identical to amino acids 28-140 of SEQ ID NO:2.

(i) "treating all neuropathic pains"

It is applicant's understanding that the amendment to claim 1 to require that the neuropathic pain treated according to the claimed method be "neuropathic pain associated with diabetic neuropathy" overcomes the present rejection insofar as it relates to the assertion that the specification "does not reasonably provide enablement for a method of treating all neuropathic pains in a subject." As indicated in the Office Action, the specification contains working examples demonstrating the effectiveness of systemic administration of neublastin in an animal model of diabetic neuropathic pain.

(ii) "administering all neublastin polypeptides"

Claim 1 has been amended to require that the "neublastin polypeptide" used in the claimed method exhibit neurotrophic activity and comprise an amino acid sequence that is at least 85% identical to amino acids 28-140 of SEQ ID NO:2. It is well within the grasp of the biologist of ordinary skill to prepare a polypeptide that is at least 85% identical to amino acids 28-140 of the neublastin sequence of SEQ ID NO:2. The specification describes standard mutagenesis methods that can be used to prepare variants and truncates of neublastin. Furthermore, the specification identifies neublastin as having seven cysteines (at positions 43, 70, 74, 107, 108, 136 and 138 in SEQ ID NO:2) that are conserved in members of the TGF-beta

superfamily. The skilled person would readily understand that retention of these cysteine residues and/or conservative substitution of individual amino acids (other than these cysteines) constitute means of preparing variants and/or truncates of neublastin that would be expected to retain bioactivity (i.e., exhibit neurotrophic activity). In view of the specification's disclosure of the amino acid sequence of human, rat, and mouse neublastin polypeptides (the alignment of which in Table 2 identifies several amino acid residues that are not conserved among all three species and can thus likely be substituted without eliminating bioactivity), combined with the knowledge in the art that conservative amino acid substitutions can be made in a protein so as to reduce the likelihood that a given amino acid change will result in a loss of function, it would have required no undue experimentation for the skilled person to prepare a polypeptide that contains an amino acid sequence that is at least 85% identical to amino acids 28-140 of SEQ ID NO:2 and that is expected to retain the neublastin biological activity recited in the claims.

The Office Action stated that "Applicant also fails to show that whether a neublastin polypeptide comprising 42-140 or 37-140 of SEQ ID NO:2 would also have the same effect as a polypeptide consisting of aa 28-140 of SEQ ID NO:2." As noted in the specification at page 11, paragraph [0038] "[i]t is understood that the truncated forms of Neublastin disclosed herein (e.g., the 112AA through 99AA forms) have neurotrophic activity." Two specific truncated forms of neublastin (NBN99, containing amino acids 42-140 of SEQ ID NO:2, and NBN104, containing amino acids 37-140 of SEQ ID NO:2) are recited in the claims. The bioactivity of these truncated forms of neublastin is described in detail in, e.g., Johansen et al., U.S. Patent Publication No. 2002/0055467 and Sah et al., U.S. Patent Publication No. 2004/0142418.

In addition to having been able to produce neublastin sequence variants having at least 85% identity to amino acids 28-140 of SEQ ID NO:2, it would have required no undue experimentation for the skilled artisan to identify those variants that retain the neublastin functional activity (i.e., neurotrophic activity) recited in the claims. Readily screenable assays for determining whether a given protein exhibits neurotrophic activity are described in, e.g., WO 00/01815 (referenced in the specification at page 8, paragraph [0032]).

The Office Action cited Burgess et al. (1990) J. Cell. Biol. 111:2129-38 ("Burgess") and two other publications in support of the assertion that "a single amino acid change can alter the function of a protein." Burgess describes the effects of selected point mutations on the functional activity of Heparin-Binding Growth Factor-1 ("HBGF-1"). For example, Burgess describes the replacement of lysine 132 of HBGF-1 with a glutamic acid residue as reducing the apparent affinity of the protein for immobilized heparin (Burgess at page 2132). The investigation by Burgess of the functional importance of selected amino acid residues of the HBGF-1 protein fails to negate the patentability of the method of claim 1. Although it is possible in certain cases to abolish the functional activity of a protein by mutating a critical amino acid residue (as described by Burgess), this in no way suggests that a person of ordinary skill in the art cannot readily make functional variants of a given protein (e.g., neublastin) without undue experimentation. The skilled person would expect that a significant percentage of even random substitutions in a given protein will result in mutated proteins with full or nearly full activity. These are far better odds than those at issue in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), in which the court found that screening many hybridomas to find the few that fell within the claims was not undue experimentation. Furthermore, as detailed herein, assays available as of the filing date of the present application permit the selection of those neublastin mutants having the activity required by the claims. The question is not whether it is possible to abolish activity of a given protein by introducing a point mutation, but rather whether one of ordinary skill can produce, without undue experimentation, mutants in which the activity is <u>not</u> abolished.

In light of the foregoing remarks, applicant respectfully submits that one of ordinary skill in the art would have been able, at the time of filing of the present application, to make and use the neublastin polypeptide recited in the claimed methods without undue experimentation and with a reasonable expectation of success. Accordingly, applicant requests that the Examiner withdraw the rejection of independent claim 1 and the claims that depend therefrom.

35 U.S.C. §112, First Paragraph (Written Description)

At pages 10-14 of the Office Action, claims 1, 2, 4, 5, 10-12, 35-37, and 57-68 were rejected as allegedly containing subject matter that was not described in the specification in such a way that one skilled in the art can reasonably conclude that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant respectfully traverses the rejection in view of the claim amendments and the following remarks.

As detailed above, amended independent claim 1 is directed to a method for treating neuropathic pain associated with diabetic neuropathy by administering to a subject, via systemic delivery, a therapeutically effective amount of a neublastin polypeptide that (i) exhibits neurotrophic activity, and (ii) comprises an amino acid sequence that is at least 85% identical to amino acids 28-140 of SEQ ID NO:2.

The genus of polypeptides encompassed by claim 1 does not have substantial variation, since all polypeptides encompassed by the genus must exhibit neurotrophic activity and contain an amino acid sequence that is at least 85% identical to amino acids 28-140 of SEQ ID NO:2. The human, rat, and mouse neublastin polypeptides disclosed in the specification (see Table 2 at page 15) are representative of the claimed genus because: all members of the claimed genus are highly similar to a reference sequence (SEQ ID NO:2); and the specification describes assays for identifying variants encompassed by the claims having the specified neurotrophic activity. In addition to disclosure of the sequences of human, rat, and mouse neublastin polypeptides (the alignment of which in Table 2 identifies specific amino acid residues at which variability may be tolerated), the specification also describes several biologically active truncated forms of neublastin lacking 1 to 14 amino acid residues at the amino terminus (see specification at page 9, paragraph [0037] to page 11, paragraph [0039]; the biological activity of these truncated forms of neublastin is described in detail in, e.g., Johansen et al., U.S. Patent Publication No. 2002/0055467 and Sah et al., U.S. Patent Publication No. 2004/0142418). Furthermore, as noted above in response to the enablement rejection, the specification identifies neublastin as having seven cysteine residues (at positions 43, 70, 74, 107, 108, 136 and 138 in SEQ ID NO:2) that are

conserved in members of the TGF-beta superfamily and that can be retained in variants and/or truncates of neublastin used in the claimed methods. In light of the disclosure contained in the application as filed, the skilled artisan would have concluded that the inventors were in possession (at the time of filing of the present application) of the necessary common attributes possessed by the members of the claimed genus.

Claim 1 is drawn to a method of using a polypeptide structurally defined by the degree of identity to a reference sequence. The claim thus provides a precise definition of the invention by structure, as is generally required for an adequate description of a protein sequence. Moreover, the claimed invention is also defined by the recited function (i.e., neurotrophic activity) of the neublastin polypeptide. The claims are not directed to a mere desired result without structure, as was the case in *Regents of the University of California v. Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997) (stating that "generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is usually an adequate description of the claimed genus."). A person of ordinary skill in the art would clearly understand the structural definition of the polypeptide provided by claim 1 and would therefore understand the inventor to have been in possession of the polypeptide recited in the claims at the time the application was filed. Accordingly, independent claim 1 and the claims that depend therefrom satisfy the written description requirement. Applicant requests that the Examiner withdraw the rejection.

Obviousness-Type Double Patenting

At pages 14-17 of the Office Action, the Examiner provisionally rejected claims 1, 2, 4, 5, 10-12, 35-37, 57, and 66-70 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over (i) claims 28 and 34 of co-pending and commonly assigned application serial number 10/356,264, and (ii) claims 15-24 of co-pending and commonly assigned application serial number 10/553,710.

The allegedly conflicting claims of application serial numbers 10/356,264 and 10/553,710 have not been patented. For this reason, the present rejection is a provisional obviousness-type double patenting rejection. In view of the amendments and remarks presented herein, it is applicant's understanding that the provisional obviousness-type double patenting rejection is the only rejection remaining in the present application. Accordingly, the double patenting rejection should be withdrawn to permit the present application to issue as a patent. See MPEP § 804.I.B. Because neither of application serial numbers 10/356,264 and 10/553,710 has issued as a patent, no terminal disclaimer is required for the present application. Applicant respectfully requests that the Examiner withdraw the rejection.

U.S.C. § 102 (Anticipation)

At pages 18-20 of the Office Action, claims 1, 2, 4, 5, 10-12, 35-37, and 57-70 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S., Patent No. 6,734,284 ("the '284 patent").

Applicant respectfully traverses the rejection in view of the following remarks.

The claimed invention is based, at least in part, upon the inventor's discovery that systemic administration of neublastin is therapeutically effective in an animal model of diabetic neuropathic pain. Consistent with this discovery, independent claim 1 is directed to a method for treating neuropathic pain associated with diabetic neuropathy by administering a neublastin polypeptide to a subject via systemic delivery.

Campbell et al. (2006) Neuron 52:77-92 ("Campbell"), a reference cited by the Office in support of the present rejection, cites Gardell et al. (2003) Nat. Med. 2003 9(11):1383-89 ("Gardell;" reference "AH" of the Information Disclosure Statement filed on July 17, 2006) for the proposition that systemic administration of neublastin (also known in the art as "artemin") dose-dependently reverses the behavioral signs of neuropathic pain in rats with spinal nerve ligation injury (Campbell at page 80, 2nd column, last paragraph). Gardell is an academic publication of experimental results contained in the present patent application. As detailed in Gardell, neublastin was the first growth factor found to be able to reverse and normalize

experimental neuropathic pain following systemic administration. In contrast to the systemic delivery of neublastin, Gardell notes that the neurotrophic factor GDNF had previously been found to reverse the behavioral consequences of neuropathic pain following continuous intrathecal administration (i.e., injection into the spinal canal).

The '284 patent describes the cloning and characterization of the neurotrophic factor neublastin. The '284 patent does not contain a working example describing administration of a neublastin polypeptide to an animal to treat neuropathic pain associated with diabetic neuropathy. The '284 patent's only working example of administration of a composition to an animal is administration of a neublastin-encoding lentivirus in a rat model of Parkinson's disease. As such, there is no disclosure in the '284 patent of a treatment that was actually performed that can be considered for possible anticipation of the claimed methods. As a result, it is applicant's understanding that the present rejection is premised upon prophetic statements contained throughout the '284 patent specification. However, as detailed below, the '284 patent does not disclose that a neublastin polypeptide can be used to treat neuropathic pain associated with diabetic neuropathy by systemic delivery of the polypeptide to a subject.

In a section entitled "Methods of Treatment" (column 20, line 15, to column 22, line 11), the '284 patent contains the following extensive description of disorders that are stated to be treatable with "polypeptides and nucleic acids of this invention" as well as peptide fragments and derivatives therefrom and antibodies.

> The disorder or disease may in particular be damages of the nervous system caused by trauma, surgery, ischemia, infection, metabolic diseases, nutritional deficiency, malignancy or toxic agents, and genetic or idiopathic processes.
>
> The damage may in particular have occurred to sensory neurons or retinal ganglion cells, including neurons in the dorsal root ganglion or in any of the following tissues: The geniculate, petrosal and nodose ganglia; the vestibuloacoustic complex of the VIIIth cranial nerve; the ventrolateral pole of the maxillomandribular lobe of the trigeminal ganglion; and the mesencephalic trigeminal nucleus.
>
> In a preferred embodiment of the method of the invention, the disease or disorder is a neurodegenerative disease involving lesioned and traumatic neurons, such as traumatic lesions of peripheral nerves, the medulla, and/or the spinal cord,

cerebral ischaemic neuronal damage, neuropathy and especially peripheral neuropathy, peripheral nerve trauma or injury, ischemic stroke, acute brain injury, acute spinal cord injury, nervous system tumors, multiple sclerosis, exposure to neurotoxins, metabolic diseases such as diabetes or renal dysfunctions and damage caused by infectious agents, neurodegenerative disorders including Alzheimer's disease, Huntington's disease, Parkinson's disease, Parkinson-Plus syndromes, progressive Supranuclear Palsy (Steele-Richardson-Olszewski Syndrome), Olivopontocerebellar Atrophy (OPCA), Shy-Drager Syndrome (multiple systems atrophy), Guamanian parkinsonism dementia complex, amyotrophic lateral sclerosis, or any other congenital or neurodegenerative disease, and memory impairment connected to dementia.

In a preferred embodiment, we contemplate treatment of sensory and/or autonomic system neurons. In another preferred embodiment, we contemplate treatment of motor neuron diseases such as amyotrophic lateral sclerosis ("ALS") and spinal muscular atrophy. In yet another preferred embodiment, we contemplate use of the neublastin molecules of this invention to enhance nerve recovery following traumatic injury. In one embodiment we contemplate use of a nerve guidance channel with a matrix containing neublastin polypeptides. Such nerve guidance channels are disclosed, e.g., U.S. Pat. No. 5,834,029, incorporated herein by reference.

In a preferred embodiment, the polypeptides and nucleic acids of this invention (and pharmaceutical compositions containing same) are used in the treatment of peripheral neuropathies. Among the peripheral neuropathies contemplated for treatment with the molecules of this invention are trauma-induced neuropathies, e.g., those caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorders related to neurodegeneration.

We also contemplate treatment of chemotherapy-induced neuropathies (such as those caused by delivery of chemotherapeutic agents, e.g., taxol or cisplatin); toxin-induced neuropathies, drug-induced neuropathies, vitamin-deficiency-induced neuropathies; idiopathic neuropathies; and diabetic neuropathies. See, e.g., U.S. Pat. Nos. 5,496,804 and 5,916,555, each herein incorporated by reference.

We also contemplate treatment of mon-neuropathies, mono-multiplex neuropathies, and poly-neuropathies, including axonal and demyelinating neuropathies, using the neublastin nucleotides and polypeptides of this invention.

> In another preferred embodiment, the polypeptides and nucleic acids of this invention (and pharmaceutical compositions containing same) are used in the treatment of various disorders in the eye, including photoreceptor loss in the retina in patients afflicted with macular degeneration, retinitis pigmentosa, glaucoma, and similar diseases.

In addition to the listing of disorders reproduced above, the "Methods of Treatment" section contains two references to routes of administration of a polypeptide. The first reference (at column 20, lines 23-26) states that "[t]he polypeptides of the present invention may be used directly via, e.g., injected, implanted or ingested pharmaceutical compositions to treat a pathological process responsive to the neublastin polypeptides." This passage contains no reference to either systemic delivery or to treatment of neuropathic pain associated with diabetic neuropathy. The second reference (at column 21, lines 24-26) refers to "use of a nerve guidance channel with a matrix containing neublastin polypeptides" and follows a sentence describing "use of the neublastin molecules of this invention to enhance nerve recovery following traumatic injury." The nerve guidance channel constitutes local, not systemic, delivery of a neublastin polypeptide.

In a separate section of the specification entitled "Pharmaceutical Compositions" (column 18, line 30 to column 20, line 14), the '284 patent specification contains the following extensive list means of administering a pharmaceutical composition to a subject:

> The pharmaceutical composition of this invention may be administered by any suitable route, including, but not limited to oral, intravenous, intramuscular, inter-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcultaneous, intraperitoneal, intranasal, anteral, topical, sublingual or rectal application, buccal, vaginal, intraorbital, intracerebral, intracranial, intraspinal, intraventricular, intracisternal, intracapsular, intrapulmonary, transmucosal, or via inhalation.

The present anticipation rejection requires selecting and combining at least the following three distinct elements from separate parts of the '284 patent specification: (i) treatment of "diabetic neuropathies" (selected from the many disorders described in the "Methods of Treatment" section); (ii) treatment with a neublastin polypeptide (selected from several neublastin compositions, including neublastin nucleic acids, expression vectors, antibodies, and antisense compositions as described in the "Methods of Treatment" section); and (iii) systemic

administration (selected from the lengthy list of administration routes provided in the "Pharmaceutical Compositions" section).

An anticipating reference must describe the claimed subject matter with sufficient clarity and detail to establish that the subject matter existed and that its existence was recognized by persons of ordinary skill in the field of the invention. *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 545 (Fed. Cir. 1998). "[T]here is no anticipation 'unless all of the same elements are found in exactly the same situation and united in the same way . . . in a single prior art reference.'" *Perkin-Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 894, 221 USPQ 669, 673 (Fed. Cir. 1984) (citing *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 771, 218 USPQ 781, 789 (Fed. Cir. 1983). The '284 patent does not clearly and unequivocally disclose the claimed subject matter or direct those skilled in the art to the claimed subject matter without need for picking, choosing, and combining various disclosures of the reference. The separate prophetic descriptions in the '284 patent of extensive lists of disorders, neublastin-related compositions that can be used to treat disorders, and routes of administration for neublastin-related compositions do not constitute a clear and unambiguous disclosure of a method for treating neuropathic pain associated with diabetic neuropathy by administering a neublastin polypeptide to a subject via systemic delivery. As a result, applicant requests that the Examiner withdraw the rejection.

At pages 20-21 of the Office Action, claims 1, 2, 4, 5, 10-12, 35-37, and 57-70 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by co-pending U.S. application number 10/356,264 ("the '264 application"; published as U.S. application number 20050142098), which was filed on January 31, 2003 and claims priority to U.S. provisional application number 60/266,071, filed on February 1, 2001.

Enclosed with this response is a declaration by the inventor stating that the subject matter of claims 1, 2, 4, 5, 10-12, 35-37, and 57-70 of the present application was invented solely by her and that, to the extent that U.S. provisional application number 60/266,071 discloses but does not

claim the subject matter of any of these claims, the prior application does not constitute invention "by another." Applicant requests that the Examiner withdraw the rejection.

35 U.S.C. § 103(a)

At pages 21-23 of the Office Action, claims 1, 2, 4, 5, 10-12, 35-37, and 57-70 were rejected as allegedly unpatentable over the '284 patent in view of U.S. Patent No. 5,414,135 ('the '135 patent').

According to the Office Action, "U.S. Patent No. 6734284 teach as set forth above but fails to teach a derivative moiety, polyethylene glycol moiety or aliphatic esters as in claims 10-12." The Office Action cited the '135 patent as allegedly describing "coupling polyethylene glycol (PEG) as in claims 10-11" and modification of proteins "by imino esters, which is one of aliphatic esters as in claim 12."

As detailed above in response to the anticipation rejection, the '284 patent does not disclose a method for treating neuropathic pain associated with diabetic neuropathy by administering a neublastin polypeptide to a subject via systemic delivery. The '135 patent was cited for its disclosure of modification of a polypeptide with a derivative moiety. However, the '135 patent provides nothing that supplements the deficiencies of the '284 or renders obvious the method of independent claim 1. Accordingly, once independent claim 1 is held allowable, the dependent claims should also be in condition for allowance. Applicant requests that the Examiner withdraw the rejection.

CONCLUSIONS

Applicant submits that all grounds for rejection have been overcome, and that all claims are in condition for allowance, which action is requested.

Enclosed is a Petition for Extension of Time. The extension of time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply other any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 13751-034001.

Respectfully submitted,

Date: July 6, 2007

Jack Brennan
Reg. No. 47,443

Fish & Richardson P.C.
Citigroup Center
52nd Floor
153 East 53rd Street
New York, New York 10022-4611
Telephone: (212) 765-5070
Facsimile: (212) 258-2291